Chronic obstructive pulmonary disease patient journey: hospitalizations as window of opportunity for extra-pulmonary intervention.

Chronic obstructive pulmonary disease patient journey: hospitalizations as window of opportunity for extra-pulmonary intervention

Mitja Lainscak[a,b], *Harry R. Gosker*[c], *and Annemie M.W.J. Schols*[c]

Purpose of review
Hospitalizations due to exacerbation of chronic obstructive pulmonary disease (COPD) are a major burden for patient and healthcare system. Extra-pulmonary needs and resulting interventions are poorly investigated.

Recent findings
COPD induces nutritional issues, body composition changes and limits patient exercise capacity. The COPD patient journey can be accelerated through exacerbations during which disease-related detrimental factors such as systemic inflammation, hypoxia, inactivity, and glucocorticosteroid treatment converge and intensify, which acutely and often irreversibly worsens patient condition. Specific needs during exacerbations reach beyond the respiratory system, thus clinicians should comprehensively evaluate patients and identify potent and feasible metabolic and anabolic intervention targets. General and specific nutritional support appear feasible and with potential to cover for the changed bodily requirements during exacerbation. Adjunctive physical exercise or neuromuscular electrical stimulation may prevent the muscle loss.

Summary
Hospitalizations should be considered as a window of opportunity for detailed patient assessment and implementation of tailored extra-pulmonary adjunctive strategies with long-term implications. Nutritional assessment and support as well as physical exercise appear promising but should be investigated in adequately designed and conducted trials.

Keywords
body composition, chronic obstructive pulmonary disease, exercise, hospitalization, nutrition, skeletal muscle

INTRODUCTION

Global burden of disease will change in decades to follow and chronic obstructive pulmonary disease (COPD) will be a major player around the globe [1]. In addition to disease-associated mortality, COPD patients take a journey of frequent exacerbations (Fig. 1) leading to disease deterioration when systemic inflammation, hypoxia, inactivity, and glucocorticosteroid treatment converge and intensify, commonly causing hospitalizations [2▪] that are main drivers of COPD-related costs [3]. Determinants of vulnerable patient phenotypes and pathophysiological mechanisms behind the clinical presentation are not well studied and remain largely unknown [4]. A number of defense mechanisms are induced that are generally phylogenetically old and serve primarily for a swift response to resolve the acute situations, but few effective drugs and procedures are available [5,6] to counteract the deleterious mechanisms that remain chronically (over)activated. Once at this stage, patients enter a disability spiral [7▪] with devastating implications for body composition, skeletal muscle function, physical performance, quality of life, and mortality, all being highly clinically relevant [8].

[a]Division of Cardiology, University Clinic of Pulmonary and Allergic Diseases Golnik, Golnik, Slovenia, [b]Applied Cachexia Research, Department of Cardiology, Charité Medical School, Campus Virchow-Klinikum, Berlin, Germany and [c]Department of Respiratory Medicine, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Center+, Maastricht, the Netherlands

Correspondence to Mitja Lainscak, MD, PhD, FESC, Associate Professor of Internal Medicine, Division of Cardiology, University Clinic Golnik, Golnik 36, SI-4204 Golnik, Slovenia. Tel: +386 31 379 533; fax: +386 4 25 69 117; e-mail: mitja.lainscak@guest.arnes.si

Curr Opin Clin Nutr Metab Care 2013, 16:278–283
DOI:10.1097/MCO.0b013e328360285d

KEY POINTS

- Hospitalizations are window of opportunity for comprehensive patient assessment to identify specific needs and therapeutic targets.
- Malnutrition, risk of malnutrition, and specific deficiencies are common in COPD and need to be treated adequately.
- COPD exacerbations mimic hypoxic inactivity, thus sufficient anabolic drive through adjunctive interventions is necessary.

Whilst for clinically stable patients evidence and resulting guidelines from well conducted studies exist [9▪,10], the applications during acute exacerbations remain scarce. This review therefore aims to briefly summarize the available knowledge about pathophysiological processes and their consequences for COPD patients during acute exacerbations. We also discuss the potential therapeutic targets during hospitalizations and ongoing research that could, in light of few respiratory treatments with prognostic implications, delay or even reverse the COPD continuum.

DEPARTURE: THE EXACERBATION-RELATED HOSPITALIZATION AND ITS CONSEQUENCES

Particularly during exacerbations, COPD-related detrimental factors such as systemic inflammation, hypoxia, inactivity, and glucocorticosteroid treatment converge and intensify [11]. Skeletal muscle is particularly prone to damage; atrophy, and a decreased oxidative phenotype develop early and soon reach irreversible stages [12▪,13]. A number of mechanisms are involved and most of them can interfere simultaneously with metabolic function, muscle mass, and performance [14]. It is important to note the complexity and interrelation of regulatory processes involved induced by various triggers including inflammation, renin-angiotensin-aldosterone, and sympathetic system induction [15▪,16▪]. Finally, we need to be aware of other organs and systems that are usually neglected, but have a major role in maintaining a metabolic balance in the body. While initially being considered as merely an energy depot, fat tissue, for instance, has recently emerged at the crossroads of many pathophysiological processes with major implications for energy turnover and anabolic/catabolic processes and an important source of persistent systemic inflammation [17]. Implications for COPD patients are numerous and reach beyond the recently described obesity paradox phenomenon [18▪]. In this context, it is important to evaluate not only whole body fat content (generally protective in chronic disease), but also its distribution throughout the body. In clinically stable COPD, abdominal visceral fat contributes to systemic inflammation independent of BMI and total fat mass [19▪], with potentially detrimental effects on skeletal muscle oxidative phenotype [20]. Most recent insight regarding molecular pathways indicates that during acute pulmonary inflammation, TNF-α-induced NF-κB activation is required for the transition to systemic inflammation and muscle atrophy [21]. This animal model study furthermore elegantly

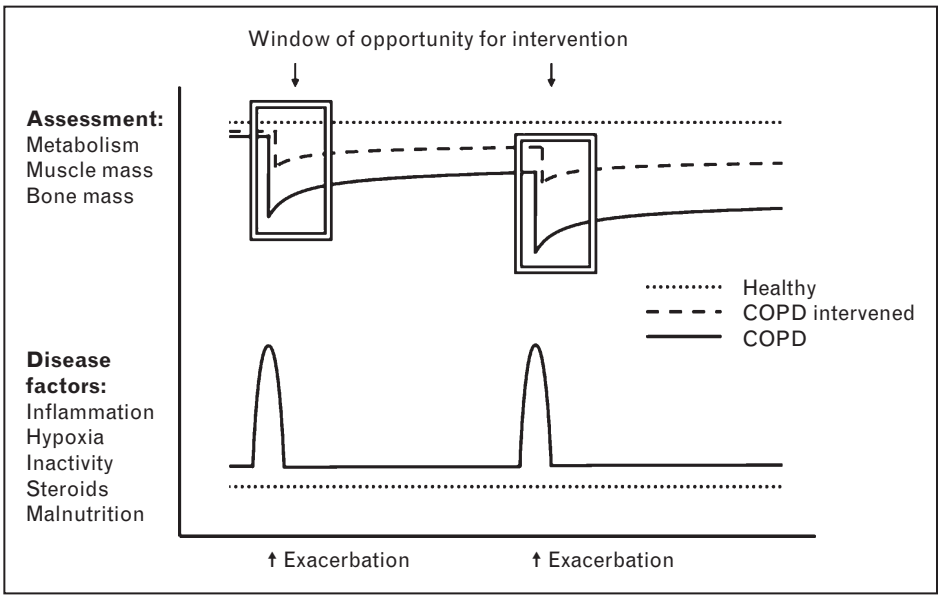

FIGURE 1. Exacerbation related hospitalizations: a window of opportunity for intervention.

demonstrated the importance of malnutrition to act hand in hand with inflammation, causing body wasting and finally an irreversible state of cachexia, out of reach of any known remedies available to date.

Acute exarcerbations and commonly administrated high-dose glucocorticosteroids induce insulin resistance, and decreased insulin sensitivity associated with a decreased muscle oxidative phenotype has also been shown in the clinically stable condition [12▪]. Some nutritional interventions could have potential to reverse inflammatory mechanisms that induce insulin resistance, but the field is not explored yet in COPD [22]. Along with activated renin-angiotensin-aldosterone system and evidence for activated peroxisome proliferator-activated receptors [23], angiotensin receptor blockers or sartanes appear to be more attractive interventions to improve the insulin resistance. Although studies in patients with COPD are scarce, Andreas *et al.* [24] demonstrated that irbesartan was well tolerated, safe, and associated with some ancillary benefits in terms of haematocrite and total lung capacity, thus setting the stage for further trials. More data are available for patients with heart failure; the analysis of large-scale Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity program ($N = 6933$) demonstrated that weight loss and being lean, particularly when combined, were important predictors for poor prognosis. The weight loss under candesartan therapy, however, was significantly less common when compared to placebo [25]. Combining this with observed pleiotropic effects through peroxisome proliferator-activated receptor activation mediated reduction of insulin resistance could deliver several benefits for the patients [26]. Indeed, in a recent placebo-controlled double-blind trial, 36 patients were treated with irbesartan or matching placebo [27]. After 4 months of treatment, insulin resistance decreased in the irbesartan (by 26%) but not the placebo group (treatment effect $P = 0.0026$). Translating the knowledge from patients with heart failure gives us reasonable ground to consider such treatment in COPD, as suggested previously [28].

CHANGE OF DIRECTION: METABOLIC NEEDS AND NUTRITIONAL SUPPORT

COPD patients have higher energy needs due to increased resting metabolic rate and whole body protein turnover, which can eventually lead to body wasting and cachexia [29]. Nutritional support has the potential to improve patient energy intake and performance [9▪,30▪]. During an exacerbation, the energy and nutrient-specific needs exceed those in stable state [31]. The subjective perception for food intake is modified (e.g. loss of appetite due to the illness) and patients may not be willing to adjust their nutritional pattern during exacerbation [32]. To investigate potential for nutritional support during hospitalization for exacerbation of COPD, a double-blind study randomized 56 nutritionally depleted patients to 3×125 ml (2.38 MJ/day) of energy and protein-rich fluid vs. matching non-caloric placebo [33]. This intervention was feasible and increased daily energy (15%) and protein (38%) intake. Considering that 14–22% of hospitalized COPD patients are malnourished or underweight, and a further 55% are at risk of malnutrition [34,35▪,36], the hospitalization should be considered as a window of opportunity to intervene, this time in a physiological manner in terms of feeding and nutritional support. We should learn from space medicine [37] and from top-level athletes [38,39] where many novel applications or nutritional compounds were tested and proved efficacious. In a stable disease, general nutritional support as part of COPD management is validated [40] in wasted COPD patients and cost-effective due to reduced hospitalizations, thus transfer to acute setting with potential extension in stable phase is warranted.

In addition to calories and proteins, a balanced daily diet should cover the daily requirements of micronutrients, vitamins, and minerals. In chronic disease, various causes increase the daily needs and those patients, including COPD, frequently present specific malnutritions, or deficiencies. The literature about these issues is generally scarce, with some recent exceptions presented but not limited to this review. Research about vitamin D has moved our interest beyond calcium and bone homeostasis to enter the field of pulmonary function with inflammation as a linking element [41]. The findings from randomized trials were eagerly expected yet the bar was apparently set too high. According to trial by Lehouck *et al.* [42▪], 100 000 IU of vitamin D supplementation every 4 weeks for 1 year in 182 patients with moderate to very severe COPD and a history of recent exacerbations generally had no effect vs. placebo on time-to-first exacerbation. Careful subgroup analysis indicates potential benefit in patients with severe vitamin D deficiency [rate of exacerbation ratio 0.57, 95% confidence interval (CI) 0.33–0.98]. Critically ill patients in need of mechanical ventilation have reduced serum levels of trace elements (selenium, manganese, zinc) and supplementation has the potential to shorten time spent with mechanical ventilation support [43]. Some confirmatory data for exacerbated COPD due to upper respiratory tract infection were published

recently. In a randomized, double-blind, placebo-controlled trial, supplementation with *Echinacea purpurea* along with zinc, selenium, and ascorbic acid for 14 days but not with *Echinacea purpurea* alone or with placebo resulted in significantly less severe and shorter exacerbation episode [44]. Importantly, intervention was safe and well tolerated with sleeping disorders occurring as most frequent adverse events. The field of micronutrient supplements appears promising with significant potential for interventional trials.

GOING THE RIGHT DIRECTION: ANABOLIC AGENTS AND PHYSICAL EXERCISE

Complementary to nutritional support are anabolic interventions, which are already implemented for patients with chronic respiratory failure [45]. Indeed, nutrients when only delivered as diet can follow different metabolic pathways according to current bodily needs. Anabolic steroids specifically induce fat free mass gain, improve exercise capacity and can restore response to rehabilitation program, blunted by the low-dose oral steroids as maintenance therapy [46]. Recent experimental evidence for synergistic effects of anabolic steroids and glucocorticoids on muscle recovery may be particularly relevant in the recovery phase from an acute exacerbation [47].

Several other modalities or nutrients have shown promising results in nonacute conditions. Amino acids as main protein components are a physiologically plausible target [48]. In COPD, the splanchnic protein extraction is reduced when compared to healthy age-matched controls. With milk protein (high branched-chain amino-acid content) supplementation, an enhanced anabolic response was observed [49▪] which could be relevant in acute situations when protein needs are increased. Substituting whey with casein proteins further enhances the effects in terms of protein anabolism, both in postprandial and exercise states [50▪▪].

The most potent physiological anabolic trigger is physical training, in particular, resistance exercise. During exacerbation, patients experience severely limited physical performance, mainly due to dyspnoea or infection. Thus, patients need to maintain a sufficient anabolic drive through adjunctive intervention, and data supporting feasibility and safety of rehabilitation during or immediately after hospitalization are emerging. In a randomized trial comparing low, moderate/high and no exercise during acute exacerbation of COPD, adherence of 80% was demonstrated and exercise was considered safe and feasible [51]. One step further Babu *et al.* [52] randomized 38 patients during acute exacerbation of COPD to regular physical therapy vs. regular and on-call physical therapy. The addition of on-call sessions increased 6-min walk distance and improved peak expiratory flow. Feasibility, safety, and effects of resistance training were investigated in a randomized trial of 40 patients hospitalized for COPD exacerbation [53]. In addition to routine physiotherapy, the intervention group performed three sets of eight repetitions of quadriceps resistance exercise that improved muscle strength and 6-min walk distance at discharge and promoted more anabolic status in skeletal muscle as investigated in biopsy samples. If the patients are too ill to follow the physiotherapy or if this is beyond available resources, transcutaneous electrical muscle stimulation can be considered. Meglic *et al.* [54▪] tested the feasibility of this method in 19 patients hospitalized due to COPD exacerbation and demonstrated good tolerability, feasibility, and safety of an average of 15 sessions per patient. Such an intervention improved quadriceps strength, which correlated to stimulation intensity during 14 sessions, without any adverse events [55]. To date, no study has investigated the molecular or histological profile of such an intervention starting at admission to hospital. The best information comes from Abdellaoui *et al.* [56▪▪] who performed skeletal muscle biopsies in 15 patients who were randomized to electrical muscle stimulation ($N = 9$) or placebo on average 12 days after hospital admission. On top of longer 6-min walk distance, they were able to demonstrate a significant increase in type I fibres proportion in patients receiving electrostimulation.

ARRIVAL: HOSPITALIZATION, THE WINDOW OF OPPORTUNITY FOR TREATMENT

The consensus of the authors is that our understanding of pathophysiological mechanisms and processes during bouts of COPD exacerbations remains insufficient. We also believe that translation from other chronic diseases (that frequently coexist), space medicine, and top-level sport is suboptimal. From physiological perspective, most attractive therapeutic targets would be defense mechanisms (e.g. sympathetic nervous system, renin-angiotensin-aldosterone system, inflammation) that are activated when exposed to acute metabolic stress. Furthermore, it seems plausible to block these systems on a long-term basis to prevent cumulating damage, which makes subclinical changes clinically important and mostly irreversible. In this context, physical activity with all direct and indirect effects appears an attractive target to focus on. Being the most effective anabolic 'remedy', it has important effects beyond physical performance. Through exercise, metabolic

processes, acute defense mechanisms, and anabolic/catabolic equilibrium are balanced to prevent the body wasting and eventually cachexia. Finally, the energy demands increase during deterioration thus nutritional support is deemed as necessary to avoid loss of the bodily reserves and tissues utilization.

CONCLUSION

Available evidence and ongoing research in the field are scarce; we, however, anticipate this will change shortly with the focus on both most feasible and most sophisticated cutting edge interventions. First step in patient assessment during exacerbation/hospitalization should be comprehensive assessment and identification of plausible intervention targets. With evidence at hand, the stage is set for exercise or muscle stimulation as a surrogate for normal daily activity where there already is some guidance about the timing and dose of the intervention. The nutritional strategies to cover for specific needs during exacerbation are less well investigated and simple translation from stable chronic disease may not be optimal. Transition of these strategies into the chronic disease state should be the next step, with particular emphasis on patient self-management. Clinicians should not, however, be too much focused on individual patients only and think more globally. Many of the suggested interventions are public health strategies to prevent and to control chronic disease. With limited funding available, the output and impact are therefore largely dependent upon joint efforts and collaborative projects where awareness about COPD, which appears poor among lay public and patients [57], and all associated consequences may be one of interim goals.

Acknowledgements

Drafting the manuscript: M.L., H.R.G, A.M.W.J.S. Part of this work has received funding from the European Union Seventh Framework Programme [FP7/2007-2013] under grant agreement n° 241558 (SICA-HF).

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 355).

1. Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. Lancet 2012; 379:1341–1351.
2. ■ Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax 2012; 67:957–963.

This study is one of the largest to analyse COPD natural history after first hospitalization for COPD.

3. Perera PN, Armstrong EP, Sherrill DL, Skrepnek GH. Acute exacerbations of COPD in the United States: inpatient burden and predictors of costs and mortality. COPD 2012; 9:131–141.
4. Hurst JR, Vestbo J, Anzueto A, *et al.* Susceptibility to exacerbations in chronic obstructive pulmoanry disease. N Engl J Med 2010; 363:1128–1138.
5. Hansel TT, Barnes PJ. New drugs for exacerbations of chronic obstructive pulmonary disease. Lancet 2009; 374:744–755.
6. Quon BS, Gan WQ, Sin DD. Contemporary management of acute exacerbations of COPD: a systematic review and metaanalysis. Chest 2008; 133:756–766.
7. ■ van de Bool C, Steiner MC. Schools AMWJ. Nutritinal targets to enhance exercise performance in chronic obstructive pulmonary disease. Curr Opin Clin Nutr Metab Care 2012; 15:553–560.

A comprehensive overview of therapeutic targets under investigation to improve patient exercise performance.

8. Laveneziana P. Palange P on behalf of the ERS Research Seminar Faculty. Physical inactivity, nutritional status and systemic inflammation in COPD. Eur Respir J 2012; 40:522–529.
9. ■ Ferreira IM, Brooks D, White J, Goldstein R. Nutritional supplementation for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2012; 12:CD000998.

Most recent comprehensive review and meta-analysis of nutritional support in COPD, demonstrating potential particularly in malnourished patients.

10. Nici L, Donner C, Wouters E, *et al.* American Thoracic Society/European Respiratory Society Statement on Pulmonary Rehabilitation. Am J Respir Crit Care Med 2006; 173:1390–1413.
11. Turan N, Kalko S, Stincone A, *et al.* A systems biology approach identifies molecular networks defining skeletal muscle abnormalities in chronic bstructive pulmonary disease. PloS Comput Biol 2011; 7:e1002129.
12. ■ van den Borst B, Slot IG, Hellwig VA, *et al.* Loss of quadriceps muscle oxidative phenotype and decreased endurance in patients with mild-to-moderate COPD. J Appl Physiol 2012. doi: 10.1152/japplphysiol.00508.2012.

This study elegantly demonstrated that muscle mass loss with reduced endurance is present already in patients with mild/moderate COPD without muscle wasting.

13. Remels AH, Gosker HR, Langen RC, Schols AM. The mechanisms of cachexia underlying muscle dysfunction in COPD. J Appl Physiol 2012. doi: 10.1152/japplphysiol.00790.2012.
14. Doehner W, von Haehling S, Anker SD, Lainscak M. Neurohormonal activation and inflammation in chronic cardiopulmonary disease: a brief systematic review. Wien Klin Wochenschr 2009; 121:293–296.
15. ■ Natanek SA, Gosker HR, Slot IG, *et al.* Pathways associated with reduced quadriceps oxidative fibres and endurance in COPD. Eur Respir J 2012 [Epub ahead of print]. doi: 10.1183/09031936.00098412.

This study used skeletal muscle biopsy samples to investigate molecular pathways in COPD patients with and without fibre shift.

16. ■ Doehner W, Haeusler KG, Endres M, *et al.* Neurological and endocrinological disorders: orphans in chronic obstructive pulmonary disease. Respir Med 2011; 105 (Suppl 1):S12–S19.

Most recent review about endocrinological disorders in COPD, focusing primarily on glucose metabolism and insulin resistance.

17. Agusti A, Edwards LD, Rennard SI, *et al.* Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. PloS One 2012; 7:e37483.
18. ■ van den Borst B, Gosker HR, Schols AM. Central fat and peripheral muscle: partners in crime in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013; 187:8–13.

A novel and intriguing hypothesis-generating study with several hot-topic points that are going to be addressed in future studies.

19. ■ van den Borst B, Gosker HR, Koster A, *et al.* The influence of abdominal visceral fat on inflammatory pathways and mortality risk in obstructive lung disease. Am J Clin Nutr 2012; 96:516–526.

An elegant study to generate the evidence of excessive abdominal fat association with increased systemic inflammatory markers.

20. Rutten EP, Breyer MK, Spruit MA, *et al.* Abdominal fat mass contributes to the systemic inflammation in chronic obstructive pulmonary disease. Clin Nutr 2010; 29:756–760.
21. Langen RC, Haegens A, Vernooy JH, *et al.* NF-κβ activation is required for the transition of pulmonary inflammation to muscle atrophy. Am J Respir Cell Mol Biol 2012; 47:288–297.
22. Hommelberg PP, Langen RC, Schols AM, *et al.* Inflammatory signaling in skeletal muscle insulin resistance: green signal for nutritional intervention? Curr Opin Clin Nutr Metab Care 2010; 13:647–655.
23. Remels AH, Schrauwen P, Broekhuizen R, *et al.* Peroxisome proliferator-activated receptor expression is reduced in skeletal muscle in COPD. Eur Respir J 2007; 30:245–252.
24. Andreas S, Herrmann-Lingen C, Raupach T, *et al.* Angiotensin II blockers in obstructive pulmonary disease: a randomised controlled trial. Eur Respir J 2006; 27:972–979.

25. Pocock SJ, McMurray JJ, Dobson J, *et al.* Weight loss and mortality risk in patients with chronic heart failure in the candesartan in heart failure: assessmen tof reduction in mortality and morbidity (CHARM) programme. Eur Heart J 2008; 29:2641–2650.

26. Schupp M, Janke J, Clasen R, *et al.* Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-gamma activity. Circulation 2004; 109:2054–2057.

27. Doehner W, Todorovic J, Kennecke C, *et al.* Improved insulin sensitivity by the angiotensin receptor antagonist irbesartan in patients with systolic heart failure: a randomized double-blinded placebo-controlled study. Int J Cardiol 2012; 161:137–142.

28. Lainscak M, Andreas S, Scanlon PD, *et al.* Ghrelin and neurohumoral antagonists in the treatment of cachexia associated with cardiopulmonary disease. Intern Med 2006; 45:837.

29. Schols AMWJ, Gosker HR. The patophysiology of cachexia in chronic obstrucitve pulmonary disease. Curr Opin Support Palliat Care 2009; 3:282–287.

30. ▪ Collins PF, Stratton RJ, Elia M. Nutritional support in chronic obstructive pulmonary disease: a systematic review and meta-analysis. Am J Clin Nutr 2012; 95:1385–1395.

This comprehensive review and meta-analysis demonstrated that oral nutritional support has potential to improve food intake and some measures of exercise performance in COPD.

31. Vermeeren MAP, Schols AMWJ, Wouters EFM. Effects of an acute exacerbation on nutritional and metabolic profile of patients with COPD. Eur Respir J 1997; 10:2264–2269.

32. Raguso CA, Luthy C. Nutritional status in chronic obstructive pulmonary disease: role of hypoxia. Nutrition 2011; 27:138–143.

33. Vermeeren MA, Wouters EF, Geraerts-Keeris AJ, Schols AM. Nutritional support in patients with chronic obstructive pulmoanry disease during hospitalisation for an acute exacerbation: a randomized controlled feasibility trial. Clin Nutr 2004; 23:1184–1192.

34. Lainscak M, von Haehling S, Doehner W, *et al.* Body mass index and prognosis in patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease. J Cachexia Sarcopenia Muscle 2011; 2:81–86.

35. ▪ Benedik B, Farkas J, Kosnik M, *et al.* Mini nutritional assessment, body composition, and hospitalisations in patients with chronic obstructive pulmonary disease. Respir Med 2011; 105 (Suppl 1):S38–S43.

This is an elegant study to compare nutritional status in healthy controls and COPD patients, reporting malnutrition or risk of malnutrition in 69%, with an association with increased risk of hospitalization.

36. Hallin R, Gudmundsson G, Suppli Ulrik C, *et al.* Nutritional status and long-term mortality in hospitalised patients with chronic obstructive pulmonary disease (COPD). Respir Med 2007; 101:1954–1960.

37. Cooper M, Douglas G, Perchonok M. Developing the NASA food system for long-duration missions. J Food Sci 2011; 76:R40–R48.

38. Jeukendrup AE. Nutrition for endurance sports: marathon, triathlon, and road cycling. J Sports Sci 2011; 29 (Suppl 1):S91–S99.

39. Stellingwerff T, Maughan RJ, Burke LM. Nutrition for power sports: middle-distance running, track cycling, rowing, canoeing/kayaking, and swinimg. J Sports Sci 2011; 29 (Suppl 1):S79–S89.

40. van Wetering CR, Hoogendoorn M, Broekhuizen R, *et al.* Efficacy and costs of nutritional rehabilitation in muscle-wasted patients with chronic obstructive pulmonary disease in a community-based setting: a prespecified subgroup analysis of the INTERCOM trial. J Am Med Dir Assoc 2010; 11:179–187.

41. Herr C, Greulich T, Koczulla RA, *et al.* The role of vitamin D in pulmonary disease: COPD, asthma, infection, and cancer. Respir Res 2011; 12:31.

42. ▪ Lehouck A, Mathieu C, Carremans C, *et al.* High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 2012; 156:105–114.

This study investigated the vitamin D supplementation and reported potential benefit in patients with severe vitamin D deficiency.

43. El-Attar M, Said M, El-Assal G, *et al.* Serum trace element levels in COPD patient: the relation between trace element supplementation and period of mechanical ventilation in a randomized controlled trial. Respirology 2009; 14:1180–1187.

44. Isbaniah F, Wiyono WH, Yunus F, *et al.* Echinacea purpurea along with zinc, selenium and vitamin C to alleviate exacerbations of chronic obstructive pulmonary disease: results from a randomized controlled trial. J Clin Pharm Ther 2011; 36:568–576.

45. Pison CM, Cano NJ, Cherion C, *et al.* Multimodal nutritional rehabilitation improves clinical outcomes of malnourished patients with chronic respiratory failure: a randomized controlled trial. Thorax 2011; 66:953–960.

46. Creutzberg EC, Wouters EF, Mostert R, *et al.* A role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo-controlled, randomized trial. Chest 2003; 124:1733–1742.

47. Pansters NA, Langen RC, Wouters E, Schols AM. Synergistic stimulation of myogenesis by glucocorticoid and IGF-I signaling. J Appl Physiol 2012. doi: 10.1152/japplphysiol.00503.2012.

48. Dioguardi FS. Clinical use of amino acids as dietary supplement: pros and cons. J Cachexia Sarcopenia Muscle 2011; 2:75–80.

49. ▪ Engelen MP, De Castro CL, Rutten EP, *et al.* Enhanced anabolic response to milk protein sip feeding in elderly subjects with COPD is associated with a reduced splanchnic extraction of multiple amino acids. Clin Nutr 2012; 31:616–624.

This study demonstrated an association between reduced splanchnic extraction of multiple amino acids and enhanced response to milk protein sip feeding.

50. ▪▪ Engelen MP, Rutten EP, De Castro CL, *et al.* Casein protein results in higher prandial and exercise induced whole body protein anabolism than whey protein in Chronic Obstructive Pulmonary Disease. Metabolism 2012; 61:1289–1300.

This was a comparative study in COPD, which demonstrated superiority of casein as compared with whey proteins in terms of protein anabolism during and after exercise.

51. Tang CY, Blackstock FC, Clarence M, Taylor NF. Early rehabilitation exercise program for inpatients during an acute exacerbation of chronic obstructive pulmonary disease: a randomized controlled trial. J Cardiopulm Rehabil Prev 2012; 32:163–169.

52. Babu AS, Noone MS, Haneef M, Samuel P. The effects of 'on-call/out of hours' physical therapy in acute exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Clin Rehabil 2010; 24:802–809.

53. Troosters T, Probst VS, Crul T, *et al.* Resistance training prevents deterioration in quadriceps muscle function during acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010; 181:1072–1077.

54. ▪ Meglic U, Sorli J, Kosnik M, Lainscak M. Feasibility of transcutaneous electrical muscle stimulation in acute exacerbation of COPD. Wien Klin Wochenschr 2011; 123:384–387.

This was the first study to demonstrate the feasibility of transcutaneous electrical muscle stimulation in patients hospitalized with exacerbated COPD.

55. Giavedoni S, Deans A, McCaughey P, *et al.* Neuromuscular electrical stimulation prevents muscle function deterioration in exacerbated COPD: a pilot study. Respir Med 2012; 106:1429–1436.

56. ▪▪ Abdellaoui A, Prefault C, Gouzi F, *et al.* Skeletal muscle effects of electrostimulation after COPD exacerbation: a pilot study. Eur Respir J 2011; 38:781–788.

This study used skeletal muscle biopsy samples to investigate effects of muscle electrostimulation after COPD exacerbation.

57. Kosmas EN, Dumitru S, Kougianos K, *et al.* Assessment of public awareness on chronic obstructive pulmonary disease in Athens, Greece, and the effects of an awareness-raising national actin plan. J Public Health Epidemiol 2011; 3:433–439.